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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/690,396	10/20/2003	Michael H. Wigler	STRATAG.7C2DV2C1	3880

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EXAMINER	
DUFFY, BRADLEY	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 08/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/690,396	WIGLER ET AL.	
	Examiner	Art Unit	
	Brad Duffy	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 December 2003 and 20 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/20/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-17 are pending and under examination.

Information Disclosure Statement

2. The date given for US Patent 4,683,195, cited on the IDS filed January 20, 2004, is incorrect. Additionally, NPL citation #12 cites the incorrect author. The examiner has corrected both citations on form PTO-892 and all references cited in the IDS have been fully considered.

Specification

3. The disclosure is objected to because of the following informalities:

a. In the first sentence, the status of Application 09/798,720 needs to be updated to indicate that it is now U.S. Patent 6,635,424.

b. In the first sentence, Application 07/919,730, now U.S. Patent 5,284,555 is an unrelated application as it is by different inventors with a different assignee and is drawn to a "PROCESS FOR PREPARING ORGANOPHOSPHINES." Please update to remove unrelated applications.

c. Although the present application appears to be in sequence compliance, the disclosure contains sequences that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2) and require sequence identifiers (i.e., SEQ ID numbers). For example, see Figure 4. It should be noted, though, that when a sequence is presented in a drawing, regardless of the format

or the manner of presentation of that sequence in the drawing, the sequence must still be included in the Sequence Listing and the sequence identifier ("SEQ ID NO:X") must be used, either in the drawing or in the Brief Description of the Drawings. See MPEP 2422.02.

Appropriate correction is required.

Claim Rejections - 35 USC § 101

4. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

5. Claims 1-17 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

The claims, as written do not sufficiently distinguish the host cell over host cells as they exist in nature because the claims do not particularly point out any non-naturally occurring differences between the claimed host cell and the structure of naturally occurring host cells. The claimed host cell producing a DNA encoding an antigen-combining protein reads upon both naturally-occuring prokaryotic and eukaryotic cells that produce DNA encoding proteins that bind a specific amino acid sequence that is also an antigen for an antibody and eukaryotic cells that naturally produce antibodies.

In the absence of the hand of man, the naturally occurring host cells are considered non-statutory subject matter (Diamond v. Chakrabadv, 206 U.S.P.Q.

193 (1980)). Amendment of the claims to recite "An isolated" host cell or similar language would obviate this rejection.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. Claims 1-17 are indefinite for reciting "DNA comprising genes," in claims 1 and 9. According to Genes IV (Lewin et al, Oxford University Press, page 810, 1990), a gene is defined as "the segment of DNA involved in producing a polypeptide chain; it includes regions preceding and following the coding regions (leader and trailer) as well as intervening sequences (introns) between individual coding segments (exons). From the teachings of the specification, however, the DNA inserted into a vector appears limited to specific antibody variable coding regions, and does not include expression control elements that fall under the definition of a gene. Accordingly, the claim is indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

9. Claims 1-17 are indefinite for reciting "antibody framework vector". The term "antibody framework vector" has divergent meanings in the art wherein it can be a vector used in subcloning antibody sequences, or a vector that has antibody constant

regions and allows antibody variable regions to be inserted. Is applicant inserting antibody sequences containing variable and constant regions into a vector, or variable regions into a vector that contains a constant region, or does the vector contain framework regions, i.e., "framework antibody vector"? Accordingly, the claim is indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. Claims 10 and 11 are indefinite in the recitation, "said DNA comprises a vector," in claim 10, whereas Claim 9 refers to "providing DNA comprising genes encoding antibodies" and "inserting the DNA into framework antibody vectors." Therefore, it is unclear whether applicant is claiming host cells comprising DNA wherein a vector is inserted into a framework antibody vector, or host cells comprising vectors into which DNA encoding antigen-combining proteins have been inserted. Similarly, Claim 11 is indefinite because it is unclear whether applicant is claiming host cells comprising DNA wherein an expression vector is inserted into a framework antibody vector, or host cells comprising expression vectors into which DNA encoding antigen-combining proteins have been inserted.

Claim Rejections - 35 USC § 112

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 1-17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The Written Description Guidelines for examination of patent applications indicates, "the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical characteristics and/or other chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show applicant was in possession of the claimed genus." (see MPEP 2163).

13. Claims 1-17 are broadly drawn to host cells, wherein the host cells have unidentified nucleic acid sequences (DNA), containing genes inserted into an antibody framework vector that is introduced into said host cell. The specification describes inserting DNA into an antibody constant region vector so that the vector then comprises an antibody variable region and a constant region in the correct order. The specification does not describe the structural elements of a gene present in these DNA sequences. For example, the specification does not describe the organization, location or actual DNA sequences of promoter and regulatory regions and introns, all defining elements of a "gene". Thus, the specification describes host cells having unidentified nucleic acid sequences (DNA), containing antibody variable regions inserted into an antibody

framework vector that is introduced into said host cell, but does not describe host cells having unidentified nucleic acid sequences (DNA), containing genes inserted into an antibody framework vector that is introduced into said host cell as claimed. The specification lacks information to lead one of skill in the art to understand that the applicant had possession of the broadly claimed invention at the time the instant application was filed. Thus, one of skill in the art would not understand that the applicant had possession of the claimed invention at the time the instant application was filed.

14. Claims 1-17 are broadly drawn to host cells, wherein the host cells contain DNA encoding antigen-combining proteins. The limitation of "antigen-combining proteins" encompasses a large genus of proteins, i.e. receptors, ligands, kinases, phosphotases, etc., that bind to antigens and not just the antibody that defines said antigen. For example, numerous antibodies are known that bind an antigen (i.e., a receptor ligand-binding site) whose structure is required for ligand-binding. Therefore, insofar as the ligand is a protein, the ligand would meet the limitation of an antigen-combining protein. Conversely, the receptor would be included in this genus, insofar as there is an antibody that targets the ligand at its receptor-binding site. Antibody-containing proteins are a sub-genus of this genus and the written description in this case only sets forth antibodies and antibody fragments that can bind antigen, as antigen-combining proteins. The specification does not envision other proteins as antigen-combining proteins.

The specification on page 7 discloses a "method of producing antigen-combining molecules (or antibodies)" and on page 21 discloses isolation of "cells producing antigen-combining molecules of selected specificity". Thus, the claims encompass an extremely large and highly variable genus of proteins including any polypeptide that binds an antigen. Additionally, there is a high degree of unpredictability in this genus as the structure of a given protein is dependent on its amino acid sequence and cannot be determined *a priori* and the function of a given protein is also highly unpredictable and variable. As for binding interactions, it is well-known in the art that they are unpredictable and have to be determined empirically, see US Patent 5,283,173, which has led to the invent of numerous methods to find protein-protein interactions, such as the yeast two-hybrid assay, immunoprecipitations and GST-fusion protein pulldowns to name a few. For inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus. See, *Eli Lilly,* 119 F.3d at 1568, 43 USPQ2d at 1406. However, written description of the present application only reasonably conveys a host cell, wherein the host cells contain DNA encoding antibodies and not the genus of "antigen-combining proteins".

Thus, the instant disclosure does not provide sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such

identifying characteristics, sufficient to show the applicant was in possession of the claimed genus of "antigen-combining proteins". See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406. The description of antibodies that bind antigen is not representative of the entire genus because the genus is highly variable, inclusive to a variety of sub-genera such as receptors, ligands, kinases, phosphotases, or any polypeptide that binds an antigen. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. Clearly, one of skill in the art would not recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the disclosed antibody sub-genus.

15. Claims 2 and 12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for prokaryotic host cells producing antibody fragments, such as F_v or Fab, does not reasonably provide enablement for the expression of whole immunoglubulins in a prokaryotic cell (i.e., *E. coli*) as broadly encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include

(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention is host cells involved in the recombinant production of functionally active immunoglobulins, particularly the use of prokaryotes as a host cell.

The claims are broadly drawn to prokaryotic host cells producing whole antibodies/immunoglubulins. Thus, the claims broadly encompass the expression of whole immunoglobulins in prokaryotic host cells.

The specification teaches that host cells will generally make both the heavy and the light chain of the immunoglobulin, "thus making it possible to prouduce complete/functional antigen-binding molecules" (pg. 11, line 9-10). The specification states "host cells will generally be cultured cells, such as myeloma cells or *E. coli*" (pg. 11, line 13-14). However, the specification does not teach how whole immunoglublins are to be produced in *E. coli*. Additionally, at the time the instant application was filed, the expression of whole immunoglublins in *E. coli* had not been reported in the art, indicating the high degree of unpredictability in the art.

The state of the art at the time of filing is such that despite numerous investigations, the expression of functional full-length antibodies has not been reported for any bacterial expression system. Simmons et al, pg 134, left column (Jour. Immun. Methods, 263:133-147, 1 May 2002). As reported by Simmons et al, pg 134, right column (Jour. Immun. Methods, supra), the first report of successful assembly of immunoglublins in *E. coli,* did not occur until after applicant's earliest priority date. Applicant has not provided any guidance or direction to assist the skilled artisan in

producing functional whole antibodies in bacterial expression systems, which according to Simmons et al (Jour. Immun. Methods, supra), published after applicant's earliest effective filing date, was the first report for any bacterial expression system. If individuals of skill in the art state that a particular invention is not possible years after the filing date that would be evidence that the disclosed invention was not possible at the time of filing and should be considered. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513-14 (Fed. Cir. 1993).

In view of the evidence that the disclosed invention was not possible at the time of filing, lack of the predictability of the art to which the invention pertains as evidenced by Simmons et al (Jour. Immun. Methods, supra), the lack of guidance and direction providing a specific and detailed description in applicant's specification of how to effectively practice the claimed immunoglobulin, and the absence of working examples, undue experimentation would be required to practice the claimed immunoglobulins with a reasonable expectation of success.

Priority

16. Applicant's claim of priority to January 11, 1990 is acknowledged, but does not comply with 37 CFR § 1.78(a). 37 CFR § 1.78(a) requires that for priority to be perfected a nonprovisional application must be copending. In the instant case, US Application 08/997,195 was abandoned August 13, 1999 and therefore was not copending with US Application 09/439,732 that was filed November 12, 1999.

Additionally, none of the other applications cited were pending on November 12, 1999. Therefore the priority date granted for this application in November 12, 1999.

Claim Rejections - 35 USC § 102

17. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

18. Claims 1, 3-11 and 13-17 are rejected under 35 U.S.C. 102(b) as being anticipated by Morrison et al (PNAS, 81:6851-6855, November 1984).

The claims are interpreted as being drawn to host cells producing DNA and antibodies, wherein the DNA encoding the antibody is inserted into a vector with that vector introduced into a host cell. The claims are also drawn to said host cells being a myeloma or plasmacytoma cell wherein said DNA is introduced by a method selected from the group consisting of: electroporation, calcium phosphate coprecipitation, protoplast fusion, viral infection and cell fusion.

Morrison et al teach host cells producing DNA and antibodies, wherein the DNA encoding the antibody is inserted into a vector, and wherein the vector is introduced into host cells (see page 6851, 1st column). Morrison et al also teach that the host cells are myeloma cells and that the DNA is introduced by protoplast fusion or calcium phosphate precipitation (see page 6851, 2nd column). Therefore, Morrison et al anticipate these claims.

19. Claims 2 and 12 are rejected under 35 U.S.C. 102(b) as being anticipated by Skerra and Pluckthun (Science 240:1038-1041, 20 May 1988, IDS filed 01/20/2004).

The claims are interpreted as being drawn to prokaryotic host cells comprising DNA encoding antibody fragments, wherein the DNA encoding the antibody is inserted into a vector and the vector is introduced into a host cell.

Skerra and Pluckthun teach prokaryotic host comprising DNA encoding an F_v antibody fragment, wherein the DNA encoding the antibody is inserted into a vector and the vector is introduced into a host cell (see abstract). Therefore, Skerra and Pluckthun anticipate these claims.

20. Claims 2 and 12 are rejected under 35 U.S.C. 102(b) as being anticipated by Better et al (Science 240:1041-1043, 20 May 1988, IDS filed 01/20/2004).

The claims and their interpretation have been described supra.

Better et al teach prokaryotic host cells comprising DNA encoding a Fab antibody fragment, wherein the DNA encoding the antibody is inserted into a vector and the vector is introduced into a host cell (see abstract). Therefore, Better et al anticipate these claims.

21. Claims 1-17 are rejected under 35 U.S.C. 102(b) as being anticipated by Wigler et al (U.S. Patent 5,780,225, published July 14, 1998, IDS filed 01/20/2004).

The claims and their interpretation have been described supra.

Wigler et al teach host cells comprising DNA encoding antibodies or antibody fragments, wherein the DNA encoding the antibody is inserted into a vector and the vector is introduced into a host cell (see page 7, 2nd column). Wigler et al also teach that the host cells can be myeloma cells, plasmacytoma cells or prokaryotic cells and that the DNA is introduced by electroporation, calcium phosphate coprecipitation, protoplast fusion, viral infection or cell fusion (see page 9, 1st column). Therefore, Wigler et al anticipate these claims.

Double Patenting

22. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In *re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

23. Claims 1-17 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 2-11 of U.S. Patent No. 6,635,424. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims only differ slightly in scope. Claims 2-11 of Patent '424 are drawn to the species, i.e., host cells comprising DNA encoding antigen-combining proteins in a vector selected from a library of DNAs, while the instant claims are drawn to the genus, i.e., host cells comprising any DNA encoding antigen-combining proteins in a vector. The genus, host cells comprising any DNA encoding antigen-combining proteins in a vector, is *prima facie* obvious in view of claims 2-11 of U.S. Patent '424 because the species, host cells comprising DNA encoding antigen-combining proteins in a vector selected from a library of DNAs, anticipates the genus of the instant application. Thus, the claims of the instant application and claims 2-11 of Patent '424 are not patentably distinct one from the other.

Conclusion

24. No claims are allowed.

25. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brad Duffy whose telephone number is (571) 272-9935. The examiner can normally be reached on Monday through Friday 7:00 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Respectfully,
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David Blanchard
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